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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,543	09/03/2003	Donna M. Shattuck	1312.03	5536

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,543	SHATTUCK ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7-9,12 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-6, 10-11, and 13-14, directed to nucleic acid analysis, and the specific polymorphism: C373T; in the reply filed on 10/19/2005 is acknowledged. The traversal is on the ground(s) that no serious burden exists to examine groups I-III together because a search relating to TBC1D1 and obesity could be used to assess the patentability of all claims. This argument has been thoroughly reviewed but is not found persuasive because each group requires different method steps and modes of operation. Accordingly, the search required to determine the patentability of diagnosis using nucleic acid based methods is different than the search to determine the patentability of diagnosis using protein based methods, which is further different from the search required to determine the patentability of methods of screening for drug candidates. A single search related to "TBC1D1 and obesity" will not provide all relevant art related to patentability as the nucleic acid is known under different synonyms. Additionally, art relating to methods of identifying nucleic acids using nucleic acid based methods would not necessarily provide any indication of identifying a protein using antibodies, for example. For example, for the methods of group II, a search relating to the predictability of identifying any of the amino acid variants with an antibody specific for the variants would need to be carried out, which is not required to for either the methods of groups I or III and would not necessarily be complete using the terms "TBC1D1 and obesity", as set forth by the response. Searching is therefore not coextensive. As the searches for each group is different, and searching more than one group represents a serious burden, the restriction is maintained. The response traverses the secondary requirement to a specific variant

and argues that the variants are related to one another by virtue of being variants of the same protein and that each variant differs from wildtype by a single nucleotide out of 2022 nucleotides. The response further asserts that sequence based searches will reveal single nucleotide substitutions and mutations in the same search. This argument has been thoroughly reviewed but was found unpersuasive. Each variant represents a different sequence, and it is this difference, not the nucleotides in common, that must be determined to assess art relevant to the patentability of the claims. A sequence search for a single sequence would not necessarily reveal all the art pertinent to patentability as TBC1D1 encompasses splice variants, representing the need to search more than one sequence. Additionally, a sequence search would not necessarily reveal all the art pertinent to patentability of the claims because mutations or single nucleotide substitutions are not necessarily submitted to nucleic acid databases. A complete search includes a search of mutation databases, such as dbSNP, as well as the patent and non patent literature for each specific mutation. As each mutation is different, and art relating to a specific variant would not necessarily provide art relating to another variant, the search for each variant is different and a search for all variants presents a serious search burden. The response's reliance on the OG notice of 11/96 is not found persuasive as the notice does not state that in all cases, 10 sequences will be searched.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. The disclosure is objected to because of the following informalities: the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable

code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3-6, 10, and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 10, and 13 recite C373T, as well as a number of other nucleotide designations and amino acid designations, however the claim provides no reference point in any sequence to determine what constitutes position 373 is, or any of the other named positions. For example, does the recitation refer to a position of a genomic sequence, or a cDNA. While the claims encompass "any TBC1D1 encoding nucleic acid molecule", the specification teaches that a number of splice variants for TBC1D1 exist, however the claim does not make clear which splice variant this designation is in reference to. Although the specification teaches that C373T can be found in SEQ ID NO: 15, it is unclear if the claim is limited to SEQ ID NO: 15 or not. It is not clear whether this mutation could also be found in other splice variants, and if so, it is unclear which nucleotide position the "C373T" designation would be. For example, Genbank Accession number NM_015173 teaches a version of an mRNA sequence with 5688 nucleotides as of September 2005 for TBC1D1. However, more than one version of the sequence exists, the first version dated October 2002 with only 2362 base pairs. With regard to genomic sequences, the

specification teaches that the TBC1D1 consensus cDNA is covered by three human genomic sequences: Genbank Accession numbers AC021106, AC009595, and AC044902. Such designation, however does not provide any clear indication of the "373" position as the specification does not teach where such position is with regard to any of the accession numbers. Even if it did, however, sequences in Genbank can be changed (as exemplified above), such that the designation of a Genbank Accession number does not provide for a fixed sequence. In the instant case, 6 different versions of AC021106 exist from January 2000 to March 2002. It is not known which version is relied on by the specification. Not only do 3 different versions of AC009595 exist, from August 1999 to June 2000, but also the accession number has been replaced by AC108933, which contains 3 different versions from February 2002 to March 2002. 2 different versions of AC044902 exist (April to May of 2000) and it has also been replaced by AC098680, which contains 3 different versions from October 2001 to February 2002. It is not known which of any of these versions is relied on by the specification. Further, with regard to SEQ ID NO: 1, for example, the instant specification lists it with 3507 nucleotides, while the '817 and '074 provisional applications list it as 3504 nucleotides. With regard to amino acid positions, Accession number NP_055988 lists two different protein versions for TBC1 member 1, the first dated October 2002 with 674 amino acids, and the second dated September 2005 with 1168 amino acids. Accordingly, absent a specific fixed sequence with which to determine the nucleotide and amino acids at the positions listed in the claims, the metes and bounds of such recitation are not clear.

Claim 6, in sections a, b, c, e, g, j, and k, lacks proper antecedent basis for the recitation of "said alterations" because the claims from which it depends only recite "an alteration", that is,

a single alteration. Accordingly, it is unclear which alterations (plural) are being referred to in the recitation of "said alterations".

5. Claims 1-6, 10-11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of determining whether a human subject is at risk for developing obesity wherein the detection of any polymorphism in any TBC1D1 encoding nucleic acid, or "C373T" in any TBC1D1 sequence, or degenerate variants of the R125W alteration, indicates that the subject is at risk for developing obesity. Additionally, the claims are drawn to a method of predicting in any individual, the likelihood of developing obesity by detecting any of three specific nucleotide variations or any variant resulting in the same amino acid substitution, in any TBC1D1 encoding nucleic acid. The claims are further drawn to analysis using genomic sequences as well as mRNA or cDNA. The specification, however, does not teach the full sequence of the TBC1D1 gene, or the genomic sequences which would be considered as a "TBC1D1 encoding nucleic acid". The specification teaches that TBC1D1 has a number of splice variants (figure 1), however the sequences of all variants do not appear to be taught. Different sequences are taught in the '817 and '074 provisional applications as well as in the prior and post filing date art, from those disclosed in the instant specification. Accordingly, not only do the claims encompass sequences which were not known in the art or taught in the

specification at the time of filing, but the designation of a specific nucleotide or amino acid is not clear based on the number of different sequences encompassed by the claims.

While the claims encompass "any TBC1D1 encoding nucleic acid molecule", the specification teaches that a number of splice variants for TBC1D1 exist, however the claim does not make clear which splice variant this designation is in reference to. Although the specification teaches that C373T can be found in SEQ ID NO: 15, it is unclear if the claim is limited to SEQ ID NO: 15 or not. It is not clear whether this mutation could also be found in other splice variants, and if so, it is unclear which nucleotide position the "C373T" designation would be.

With regard to whether specific polymorphisms exist in other splice variants, the specification teaches that "C373T" is found in SEQ ID NO: 15 while "T683G", for example, is taught in SEQ ID NO: 17. Are SEQ ID NO: 15 and 17 different versions of the same splice variant, the difference being each designated mutation, or are they different splice variants?

With regard to designations of nucleotide positions in any TBC1D1 encoding nucleic acid, Genbank Accession number NM_015173 teaches a version of an mRNA sequence with 5688 nucleotides as of September 2005 for TBC1D1. However, more than one version of the sequence exists, the first version dated October 2002 with only 2362 base pairs. With regard to genomic sequences, the specification teaches that the TBC1D1 consensus cDNA is covered by three human genomic sequences: Genbank Accession numbers AC021106, AC009595, and AC044902. Such designation, however does not provide any clear indication of the "373" position as the specification does not teach where such position is with regard to any of the accession numbers. Even if it did, however, sequences in Genbank can be changed (as exemplified above), such that the designation of a Genbank Accession number does not provide

for a fixed sequence. In the instant case, 6 different versions of AC021106 exist from January 2000 to March 2002. It is not known which version is relied on by the specification. Not only do 3 different versions of AC009595 exist, from August 1999 to June 2000, but also the accession number has been replaced by AC108933, which contains 3 different versions from February 2002 to March 2002. 2 different versions of AC044902 exist (April to May of 2000) and it has also been replaced by AC098680, which contains 3 different versions from October 2001 to February 2002. It is not known which of any of these versions is relied on by the specification. Further, with regard to SEQ ID NO: 1, for example, the instant specification lists it with 3507 nucleotides, while the '817 and '074 provisional applications list it as 3504 nucleotides. With regard to amino acid positions, Accession number NP_055988 lists two different protein versions for TBC1 member 1, the first dated October 2002 with 674 amino acids, and the second dated September 2005 with 1168 amino acids. Accordingly, the claims encompass sequences which have not been taught or described by the specification or the prior art. Further, with regard to analysis of cDNA or mRNA, the specification does not teach whether the "C373T" polymorphism is found in any TBC1D1 splice variant, it only teaches that "C373T" is found in SEQ ID NO: 15. Therefore, it is not clear whether the polymorphism designated as "C373T" is representative of the genus of TBC1D1 sequences encompassed by the claims.

Further, all of the current claims encompass a large genus of nucleic acids which comprise polymorphisms in any TBC1D1 encoding nucleic acid sequence, which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification. This large genus is represented in

the specification by only the particularly named 3 polymorphisms for which data is provided demonstrating an association with the obesity. Thus, applicant has express possession of only 3 particular polymorphisms, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with risk of developing obesity is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Even in the narrower dependent claims, such as claim 3, the claims encompass any nucleotide variants resulting in a specific amino acid substitution, however only a specific nucleotide change has been taught in the specification. No predictable correlation between the structural alteration in the amino acid R125W variant and a risk for developing obesity is provided by the specification. At page 54, the specification teaches that R125 is conserved in mice and is in the phoshotyrosine interacting domain. However, the specification provides no evidence that any nucleotide change resulting in the R125W alteration at this position, in either mice or human sequences, provides a predictable association with risk for developing obesity. The specification teaches that this specific "C373T" polymorphism was found in 22 control chromosomes. Thus it is unclear whether the association between the presence of such polymorphism "C373T" and risk for developing obesity it due to linkage with another disease causing or disease associated mutation or polymorphism, whether such "C373T"

polymorphism in obese patients was due to it's presence in a larger disease associated haplotype which is absent in the control chromosomes, or if in fact, the change from Arg to Trp at position 125 is a mutation which alters the activity of TBC1D1 in some way and therefore increases the chances of a human subject developing obesity. With regard to claim 13, the claim also encompasses analysis in any individual, which encompass non human species. However, the specification provides no predictable correlation that the polymorphism "C373T" exists in any TBC1D1 encoding nucleic acid from any species.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with an increased risk for obesity. The polymorphisms shown are not representative of the genus of any polymorphism associated with an increased risk for developing obesity because it is not clear which polymorphisms within "any" TBC1D1 encoding nucleic acid sequence would have the same affect. It is not clear whether the polymorphisms shown affect the function of TBC1D1 or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in an increased risk for obesity may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity. Although the specification teaches that the R125W mutation is in the PID domain in mice, the specification does not teach how this domain or the specific mutation are involved with obesity. The specification is also silent with regard to any structure/function correlation with regard to the remaining 2 polymorphisms listed.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

6. Claims 1-6, 10-11, 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of determining whether a human subject is at risk for developing obesity wherein the detection of any polymorphism in any TBC1D1 encoding nucleic acid, or "C373T" in any TBC1D1 sequence, or degenerate variants of the R125W alteration, indicates that the subject is at risk for developing obesity. Additionally, the claims are drawn to a method of predicting in any individual, the likelihood of developing obesity by detecting any of three specific nucleotide variations or any variant resulting in the same amino acid substitution, in any TBC1D1 encoding nucleic acid. The claims are further drawn to analysis using genomic sequences as well as mRNA or cDNA.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any TBC1D1 encoding nucleic acid and a human subjects risk for developing obesity, or between specific polymorphisms and any individuals likelihood of developing obesity.

The specification teaches (pages 53-54) that TBC1D1 is the founding member of a family of proteins with homology to tre-2/UPS6,BUB2, and cdc16 and contains a TBC box motif. The specification teaches that in mice, TBC1 showed differential expression in two mast cell lines. However, the specification does not teach the function or role of TBC1D1 in obesity and does not teach how it's function, an alteration in function, or absence of function, is associated with obesity. The specification asserts that the diagnostic/prognostic methods include determining the presence or absence of a substitution, deletion, insertion, or truncation in the PID or TBC domain of TBC1D1. However, the specification provides no predictable correlation that the presence or

absence of "any" mutation in either of these two domains is associated with obesity. Although the specification asserts that Arg125, Lys119, Ser112, and Ser28 (relative to SEQ ID NO: 2) can be critical to the PID domain's optimal interaction with phosphotyrosine, the specification does not teach what role, if any, these amino acids or domains have with regard to obesity. Additionally, it is not clear that all such amino acids would be found in the large number of different TBC1D1 splice variants.

The specification teaches the identification of 3 nucleotide polymorphisms, "C373T," "T683G" and "C1174G", in obesity linked families (page 54), but does not teach which sequence these polymorphisms were found in. For example, the specification teaches that "C373T" is found in SEQ ID NO: 15 while "T683G", is taught in SEQ ID NO: 17. Are SEQ ID NO: 15 and 17 different versions of the same splice variant, the difference being each designated mutation, or are they different splice variants? Additionally, the claims are silent with regard to a reference point for such nucleotide positions. Although the specification teaches that C373T can be found in SEQ ID NO: 15, it is unclear if the claim is limited to SEQ ID NO: 15 or not. It is not clear whether this mutation could also be found in other splice variants, and if so, it is unclear which nucleotide position the "C373T" designation would be. For example, Genbank Accession number NM_015173 teaches a version of an mRNA sequence with 5688 nucleotides as of September 2005 for TBC1D1. However, more than one version of the sequence exist, the first version dated October 2002 with only 2362 base pairs. With regard to genomic sequences, the specification teaches that the TBC1D1 consensus cDNA is covered by three human genomic sequences: Genbank Accession numbers AC021106, AC009595, and AC044902. Such designation, however does not provide any clear indication of the "373" position as the

specification does not teach where such position is with regard to any of the accession numbers. Even if it did, however, sequences in Genbank can be changed (as exemplified above), such that the designation of a Genbank Accession number does not provide for a fixed sequence. In the instant case, 6 different versions of AC021106 exist from January 2000 to March 2002. It is not known which version is relied on by the specification. Not only do 3 different versions of AC009595 exist, from August 1999 to June 2000, but the accession number has been replaced by AC108933, which contains 3 different versions from February 2002 to March 2002. 2 different versions of AC044902 exist (April to May of 2000) and it has also been replaced by AC098680, which contains 3 different versions from October 2001 to February 2002. It is not known which of any of these versions is relied on by the specification. Further, with regard to SEQ ID NO: 1, for example, the instant specification lists it with 3507 nucleotides, while the '817 and '074 provisional applications list it as 3504 nucleotides. With regard to amino acid positions, Accession number NP_055988 lists two different protein versions for TBC1 member 1, the first dated October 2002 with 674 amino acids, and the second dated September 2005 with 1168 amino acids. Accordingly, the claims encompass sequences which have not been taught or described by the specification or the prior art. Further, with regard to analysis of cDNA or mRNA, the specification does not teach whether the "C373T" polymorphism is found in any TBC1D1 splice variant, it only teaches that "C373T" is found in SEQ ID NO: 15. Therefore, it is not clear whether the polymorphism designated as "C373T" exists in all TBC1D1 sequences.

The specification provides no predictable association that broadly "any" alteration, in "any" TBC1D1 encoding nucleic acid, in "any" individual, is associated with increased risk for developing obesity. No common element or attributes of the sequences are disclosed which

would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with risk of developing obesity is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Even in the narrower dependent claims, such as claim 3, the claims encompass any nucleotide variants resulting in a specific amino acid substitution, however only a specific nucleotide change has been taught in the specification. No predictable correlation between the structural alteration in the amino acid R125W variant and a risk for developing obesity is provided by the specification. At page 54, the specification teaches that R125 is conserved in mice and is in the phoshotyrosine interacting domain. However, the specification provides no evidence that any nucleotide change resulting in the R125W alteration at this position, in either mice or human sequences, provides a predictable association with risk for developing obesity. The specification teaches that this specific "C373T" polymorphism was found in 22 control chromosomes. Thus it is not predictable whether the association between the presence of such polymorphism "C373T" and risk for developing obesity it due to linkage with another disease causing or disease associated mutation or polymorphism, whether such "C373T" polymorphism in obese patients was due to it's presence in a larger disease associated haplotype which is absent in the control chromosomes, or if in fact, the change from Arg to Trp at position 125 is a mutation which alters the activity of TBC1D1 in some way and therefore increases the chances of a human subject developing obesity. With regard to claim 13, the claim also

encompasses analysis in any individual, which encompass non human species. However, the specification provides no predictable correlation that the polymorphism "C373T" exists in any TBC1D1 encoding nucleic acid from any species. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with an increased risk for obesity. The polymorphisms shown are not representative of the genus of any polymorphism associated with an increased risk for developing obesity because it is not clear which polymorphisms within "any" TBC1D1 encoding nucleic acid sequence would have the same affect. It is not clear whether the polymorphisms shown affect the function of TBC1D1 or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in an increased risk for obesity may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity. Although the specification teaches that the R125W mutation is in the PID domain in mice, the specification does not teach how this domain or the specific mutation are involved with obesity. The specification is also silent with regard to any structure/function correlation with regard to the remaining 2 polymorphisms listed.

The art does not teach the function of the TBC1D1 protein splice variants, how they are involved in obesity, or how alterations in such are associated with obesity.

The quantity of experimentation in this area is extremely large as it requires analysis of each position in any TBC1D1 encoding sequence to determine whether any alteration at each position is associated with increased risk for developing obesity. As neither the art nor the

specification provide guidance as to which alterations at positions throughout TBC1D1 are associated with an increased risk for developing obesity, or which positions throughout TBC1D1 are critical to the function of TBC1D1 in relation to obesity, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in TBC1D1 represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Zon et al (US Patent 5,700,927) teaches analysis of expression of a gene, TBC1, for leukemias and spermatogenesis disorders.

Blumenfeld et al (Us Patent 6,825,004) teaches analysis of biallelic markers for a gene, TBC-1, in relation to prostate cancer.

8. No claims are in condition for allowance.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634
1/6/06